Claims 51 and 52 have been added. Such amendments have been made solely for the purposes of expediting prosecution, and without conceding the correctness of the Examiner's rejection, or prejudicing Applicants' right to pursue canceled subject matter in a future application. Applicants submit that support for such amendments is found *inter alia* on pages 24-26 of the originally filed specification. Accordingly, no new matter is added by this Amendment, and entry thereof and reconsideration of the claims in light of the following remarks is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1 and 6 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Specifically, the Examiner objected to the use of the term "biologics" and further objected to the recitation of the species "fatty acid esters of lactic acid" and "fatty acid esters of glycolic acid" within the same Markush group as the genus "fatty acid esters". By the present amendment, the term "biologics" has been removed from Claim 1, and a list of agents taught to be specific examples of "biologics" on pg. 26 of the specification has been substituted therefor. Further, the lactic and glycolic fatty acid ester species have been removed from the claim. Additionally, Claim 6 has been amended to correct the typographical error discovered by the Examiner, and Applicants thank the Examiner for bringing such to their attention. Accordingly, Applicants respectfully submit that the present claim amendments render this rejection moot.

35 U.S.C. § 103

The Examiner has rejected Claims 1-28 under 35 U.S.C. § 103 as allegedly obvious in view of any one of U.S. Patent No. 6,352,715, (hereinafter "'715 patent"), U.S. Patent No. 6,159,986, (hereinafter "'986 patent") or Chinese Patent No. 1,111,987 (hereinafter "'987 patent"). Further, Claims 1-28 have been rejected as allegedly obvious over any one of the above-recited references further in view of U.S. Patent No. 6,019,988 (hereinafter "'988 patent). Applicants respectfully submit that the rejected claims are patentable over the cited references for the reasons set forth below, and that the rejection should be withdrawn.

Before discussing the rejection, it is thought proper to briefly state what is required to sustain such a rejection. The issue under § 103 is whether the PTO has stated a case of *prima facie* obviousness. "The PTO has the burden under § 103 to establish a *prima facie* case of obviousness." In re Fine, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To satisfy this burden, the PTO must meet the criteria set out in M.P.E.P § 706.02(j):

> . . . three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Moreover, the obviousness analysis must comply with the statutory scheme as explained by the Supreme Court in Graham v. John Deere Co., 383 U.S. 1, 17 (1966), namely, consideration must be given to: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, (3) the level of ordinary skill in the pertinent art, and (4) additional evidence, which may serve as indicia of non-obviousness.

With the above background in mind, Applicants contend that the Examiner has failed to meet establish a *prima facie* case of obviousness. Specifically, the Office has failed to show each and every element of the present invention in the asserted references, or combination of references. Further, the Examiner has failed to show sufficient motivation for any of the asserted references to be modified or combined as stated. Finally, Applicants contend that there is an insufficient likelihood of successfully attaining a functional product using the asserted combination of references in view of the teachings of each reference as a whole.

Applicants' Invention

As recited in amended Claim 1, Applicants' invention resides in a transdermal formulation for improving memory and cognitive function which includes an amount of huperzine sufficient to achieve a huperzine blood plasma level of from about 0.1 to about 30 ng/ml. The composition additionally includes a inert carrier, and a permeation enhancer selected from the group consisting of: fatty acids, fatty acid esters, fatty alcohols, amides, amines, pyrrolidones, terpenes, surfactants, complexing agents, L-α-amino acids, lecithin, phospholipids, their salts, and mixtures thereof.

The '715 Patent

The '715 patent discloses a transdermal drug system whereby Huperzine A is administered for the treatment of Alzheimer's Disease. *See, Abstract.* The transdermal systems disclosed includes both reservoir type devices and adhesive matrix devices. *See, col. 2, ln. 56-col. 3, ln. 21.* While a number of traditional transdermal device components are seemingly contemplated, nothing expressly teaches the use of penetration enhancers as an individual effective means of enhancing Huperzine administration. Rather, the problematic issue in this patent is to attain a pH in the transdermal

delivery device that provides enhanced penetration of Huperzine into the skin. *See, col.2, ln. 65-col. 3, ln. 1.* Such a pH range for Huperzine is taught to be between 7 and 9. *See, col. 3, ln. 5-6; col. 3, ln. 20-21; Figs. 4 and 5; Table 1 at col. 7-8; col. 8, ln. 39-39-44; Claims 1, 5, 6, 10, 11, and 15.* The improved skin penetration is taught to be the result of converting Huperzine A from its ionized form at acidic pH, to its lipophilic form at a more neutral pH, which increases its skin partitioning coefficient. *See, col.8, ln. 24-37.* The reference further teaches that only the neutral species of Huperzine A is permeable to the skin. *See, col. 8, ln. 36-37.*

Further, this reference provides both an endorsement and a caution with respect to the use of co-solvents to improve the delivery of Huperzine A. Co-solvents are seemingly suggested as possibly improving the penetration of the neutral form of Huperzine, at col. 8, ln. 65-68. However, the patent also teaches that not all co-solvents may be used to effectively enhance skin permeation. Specifically, col. 8, ln. 47-52 teaches that careful evaluation of co-solvents, especially non-polar solvents, such as alcohols and glycols must be made before use, as such solvents may actually reduce the partitioning coefficient of Huperzine A, and thereby reduce its penetration into the skin.

The '986 Patent

The '986 patent discloses the use of an herbal supplement for the improvement of memory. Specifically, acetylcholine boosters, such as Huperzine A are used. *See, col. 1, ln. 34-39.* More specifically, this patent discloses the coadministration of Huperzine A with a second component extracted from a suitable plant, such as an extract of hypercum perforatum (i.e. St. John's Wort) in order to attain improved efficacy. *See, col. 1, ln. 39-43; col. 2, ln. 15-27.* While the herbal supplement is to be primarily formulated for oral delivery, other forms of administration, including

transdermal delivery are briefly mentioned. *See, col. 2, ln. 54-63.*

The '987 Patent

This abstract of this Chinese patent as cited by the Examiner teaches a plaster for treating senile dementia containing Huperzine and laurocapram or a mixture of laurocapram and another agent as a permeation enhancer.

The '988 Patent

The problematic issue in this reference is the inability to utilize various drugs with penetration enhancers due to the instability of such combinations in a single formulation over time. *See, Abstract; col. 2, ln.19-33* . As a solution to this problem, the reference teaches special devices and methods for storing and applying various compositions to the skin. In fact, the reference is replete with teachings of various devices that keep the drug and penetration enhancer elements separate until application of these elements to the skin. *See, col. 2, ln. 64-col. 3, ln. 6; col. 3, ln. 9-18; col. 3, ln. 25-33; col. 3, ln. 38-43; col. 5, ln. 38-43; col. 6, ln. 6-10;col. 6, ln. 44-65; Figs. 1-4, col. 13, ln. 26-col. 14, ln. 12.* The reference contains a long laundry list of possible drugs for use with the disclosed system and method. *See, col. 18, ln. 29-col. 19, ln. 33.* Moreover, a long laundry list of permeation enhancers for possible use with the disclosed system and method is contained at col. 20, ln. 44-67. However, the only specific drug and enhancer elements identified as having compatibility issues are a di-acid phospholipase A2 inhibitor composition and a dodecyl-N,N-diethylamino acetate enhancer. *See, col. 17, ln.33-43.*

Non-obviousness

As noted above, the invention of Claim 1 recites the use of a selected list of penetration

enhancers in combination with Huperzine in a transdermal formulation in order to achieve specified Huperzine blood plasma levels of from about 0.1 to about 30 ng/ml. Nothing in any of the references cited by the Examiner teaches or suggests these specific Huperzine blood plasma levels, let alone the specific combination of these enhancers with Huperzine in order to transdermally achieve such blood plasma levels. In fact, the Examiner admits this to be the case. In order to remedy such deficiency, the Examiner alleges that many of the specifically recited enhancers are well known as permeation enhancers and widely used in the transdermal art. Further, the Examiner alleges that it is within the skill in the art to adjust the amount of drug in order to achieve a therapeutic blood level for a predetermined period. *See, Office Action paper no. 7, section 9, pg. 6.*

Applicants respectfully disagree. In fact, it is well known in the art that penetration enhancers are idiosyncratic, and may work well for one drug and not work well for other drugs, even closely related ones. No "universal" penetration enhancer exists. Furthermore, while a penetration enhancer may actually enhance the penetration of a drug across the skin, a number of additional factors dictate whether the penetration enhancer is truly suitable for use in a given transdermal formulation, such as the compatibility of the drug with the enhancer when stored over time. Evidence that one of ordinary skill in the art would have such an understanding concerning the nature of drugs and permeation enhancers is provided by the '988 patent which focuses entirely on a solution for such issues. For example, at col. 2, ln. 43-48 states in relevant part:

> Accordingly, in view of the foregoing, and because, upon storage, the permeation enhancer degrades the drug in question, or vice versa, one skilled in the art would be led away from using....particular drugs with particular permeation enhancers, and vice versa.

Further, col. 2, ln. 51-63 discusses incompatibility issues of permeation enhancers with certain drugs

despite their ability to produce a permeation enhancing effect, and concludes that:

> As a consequence, one skilled in the art is hampered by an inability to employ certain permeation enhancers for increasing skin permeation of a drug, if the permeation enhancer and the drug cannot be mixed and stored together in a pharmaceutical composition without the permeation enhancer becoming unstable over time and degrading to produce unwanted and potentially harmful products.

While the penetration enhancers recited in Claim 1 may indeed be known as penetration enhancers for selected drugs, they are not known as penetration enhancers for all drugs, nor for Huperzine. The Examiner has failed to produce any reference that teaches transdermal penetration enhancement of Huperzine with any of the penetration enhancers recited in Claim 1. While the '988 patent happens to contain a laundry list of drugs that includes the recitation of the genus acetylcholine esterase (ACE) inhibitors, and also includes a laundry list of enhancers, such a vague recitation of these elements is insufficient to teach or suggest with the requisite specificity, the efficacy of the recited enhancers with Huperzine.

As such, nothing in any of the references asserted by the Examiner either separately, or in combination fairly teaches or suggests each and every element of amended Claim 1. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, and Applicants respectfully request that the rejection be withdrawn.

In addition, Applicants contend that none of the cited references provides a sufficient teaching or suggestion to be modified or combined as asserted by the Examiner in order to arrive at the present invention. Particularly, as recited above, the '715 patent teaches a transdermal Huperzine system that depends upon pH for optimal permeation enhancement, rather than utilizing a traditional permeation enhancer. Moreover, contrary to the Examiner's assertion that a combination of co-

solvents are taught to increase the skin permeation of Huperzine, col. 8, ln. 49-52 teaches that co-solvents need to be carefully selected in order to keep from actually hindering permeation enhancement.

Even assuming *arguendo* that the '715 reference broadly taught that a combination of co-solvents enhances the transdermal penetration of Huperzine as the Examiner asserts, the reference fails to teach or suggest any specific solvents or co-solvents. The general assertion that co-solvents enhance the penetration of Huperzine is insufficient to motivate one of ordinary skill in the art to look to the specific penetration enhancers recited by Claim 1, in order to achieve the Huperzine blood plasma concentration recited by Claim 1. Accordingly, Applicants contend that the Examiner's assertion that one of ordinary skill in the art would be motivated to utilize the enhancer recited in Claim 1 simply because many of the compounds are "known to act as permeation enhancers" is at most an allegation of "obvious to try". Moreover, in view of the dominant teaching in the '715 patent that pH is responsible for penetration enhancement, that many co-solvents could actually decrease penetration, and that any suggestion of using co-solvents is in addition to optimized pH, Applicants contend that the '715 patent actually teaches away from the present invention which relies solely on certain recited agents for penetration enhancement.

As the '715 reference falls short of the required standard to be modified as asserted by the Examiner, and actually teaches away from the present invention, Applicants submit that the only way in which one of ordinary skill in the art would arrive at the proposed modification is through hindsight after having the benefit of seeing Applicants' disclosure. In view of the foregoing, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, and

respectfully request that the rejection be withdrawn.

Neither does the '987 patent contain sufficient motivation to be modified as asserted by the Examiner in order to arrive at Applicants' invention. Specifically, the only enhancer taught for use by this reference for transdermal enhancement of Huperzine is laurocapram. Laurocapram is well known in the art under the common name Azone. This agent, while known as a good penetration enhancer for certain compounds, is also known to cause an extremely high amount of skin irritation when used as a transdermal penetration enhancer. Moreover, the issues with Azone cross beyond simple skin irritation into actual irreversible skin damage and scarring. As a result, this agent has never been approved by the United State Food and Drug Administration for use as a penetration enhancer. Notably, this substance is specifically taught as unsuitable for use in the present invention at pg. 23-24 of the present specification. As a result, the '987 reference actually teaches away from the present invention, and Applicants submit that one of ordinary skill in the art would only contemplate the modification asserted by the Examiner after viewing the present patent application using hindsight reconstruction.

Even assuming *arguendo* that Azone was considered to be viable permeation enhancer for Huperzine, nothing in the '987 reference teaches or suggests that any other enhancers can be substituted for Azone, let alone the specific list of agents required by Claim 1. To this end, the arguments raised above with respect to the idiosyncracies of permeation enhancers, and the inability to predictably exchange one for another are pertinent here. As a result, Applicants submit that the Examiner has failed to show that the '987 reference contains adequate teaching or suggestion to be modified as asserted, and therefore, the Examiner's proposed substitution of the agents recited in

Claim 1 for Azone at most amounts to an allegation of "obvious to try".

Applicants submit that in view of the foregoing, the Examiner has failed to establish a *prima facie* case of obviousness, and respectfully request that the rejection be withdrawn.

The '986 patent also fails to provide sufficient teaching or suggestion to be modified as asserted by the Examiner to arrive at the present invention. In fact, the only relevance of this reference is that it teaches administration of Huperzine A in order treat memory loss. However, this reference focuses primarily on herbal supplements containing an acetylcholine booster, such as Huperzine in combination with another agent, such as St. John's Wort in order to attain a synergistic or enhances effect. *See, col. 2, ln. 15-27.* Moreover, the primary route of administration contemplated is oral administration, with transdermal administration only being mentioned as a possibility in a list of other superficially contemplated administration routes. *See, col. 2, ln. 60-63.* No specific transdermal formulations are taught or suggested. Moreover, no mention whatsoever is made of utilizing any penetration enhancer as part of a transdermal administration formulation, let alone one of the enhancer agents specifically recited in Claim 1.

In view of the absence of any substantive teachings of a transdermal formulation, and further in view of the absence of any penetration enhancer teachings, Applicants submit that one of ordinary skill in the art would find no motivation to modify the '986 reference as asserted by the Examiner absent the hindsight benefit of a prior view of the present patent application. As a result, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, and respectfully request that the rejection be withdrawn.

The Examiner has additionally alleged that the present claims are obvious in view of the

combination of any one of the above-recited reference further in view of the '988 patent. Applicants respectfully disagree. Specifically, none of the above recited reference, nor the '988 patent contains sufficient motivation for such a combination. As noted above, the '988 reference primarily focuses on a delivery system and method for allowing otherwise incompatible drugs and enhancers to be used together. Broad lists of drugs and penetration enhancers are disclosed, but with one exception not concerning Huperzine, no teaching or suggestion of pairing any specific drug with any specific enhancer is made. Moreover, Huperzine per se is not disclosed, but rather only the genus to which Huperzine belongs, acetylcholinesterase inhibitors is taught. As such, no common teaching of transdermal Huperzine administration is found between the references and cannot be considered a basis for the combination thereof. Further, each of the points raised above concerning the insufficiency of the teachings or suggestion in the '715, '987, and '986 references to be modified by as asserted by the Examiner is equally applicable to the asserted combination of these reference with the '988 reference. In other words, the teachings of the '988 patent do not make up for the deficiencies with respect to a teaching or suggestion in the other patents, and the combination of the references is no better than the modifications alleged by the Examiner. Accordingly, the presently asserted combination of references amounts at most to an allegation of "obvious to try", and would only be made by one of ordinary skill in the art using the hindsight benefit of a prior review of the present invention.

For at least these reasons, Applicants submit that the combination of references is improper, and that no *prima facie* case of obviousness has been established. Therefore, Applicants respectfully request that the rejection be withdrawn.

In addition, it is well established that a reference must be considered for what it teaches as a whole. Therefore, even assuming *arguendo* that the '988 reference did reasonably teach or suggest the transdermal delivery of Huperzine with a permeation enhancer, the overall teachings of the reference would lead one of ordinary skill in the art away from combination with any of the other asserted references if construed to teach traditional transdermal Huperzine formulations as the Examiner asserts. Particularly, as noted above, the '988 reference primarily focuses on delivery systems that can be used to deliver drugs with permeation enhancers that would normally present an unstable and therefore unusable combination. Therefore, one of ordinary skill in the art would understand acetylcholinesterase inhibitors, including Huperzine, to be unstable when stored in the presence of the listed enhancers, and that such a combination requires the use of the special devices disclosed. Such teachings provide no motivation for combination with, and in fact teach away from, the traditional transdermal formulations taught by the other references, wherein drug and enhancer are both stored as a permanent mixture. As a result, one of ordinary skill in the art would not attempt to make such a combination absent a prior view of the present application. Such hindsight reconstruction is impermissible, and Applicants respectfully submit that no *prima facie* case of obviousness has been established, and respectfully request that the rejection be withdrawn.

CONCLUSION

In conclusion, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 112, second paragraph is moot in view of the present amendments, and that such amended and new claims are full supported by the original specification and thus present no new matter. Further, Applicants submit that the rejection under 35 U.S.C. § 103 is improper and that no *prima facie* case of obviousness has been established. Specifically, no motivation exists for the modification or combination of the cited references as asserted by the Examiner. Moreover, such modifications or combinations amount at most to allegations of "obvious to try" and hindsight reconstruction of the references would be necessary for one of ordinary skill in the art to find motivation to arrive at the asserted conclusions.

If any impediment remains to prompt allowance of the claims after consideration of the above-recited amendments and remarks, which could be alleviated during a telephone interview, the Examiner is invited to telephone Mr. David Osborne of this office, or in his absence, the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 20-0100.

DATED this 18th day of March 2003.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Once Amended) A transdermal formulation for improving memory and cognitive function comprising:

a) an amount of huperzine sufficient to achieve a huperzine blood plasma level of from about 0.1 to about 30 ng/ml;

b) an inert carrier; and

c) a permeation enhancer selected from the group consisting of: fatty acids, fatty acid esters, fatty alcohols, [fatty acid esters of lactic acid, fatty acid esters of glycolic acid,] amides, amines, pyrrolidones, [glycerol trimesters,] terpenes, surfactants, complexing agents, [biologics,] L-α-amino acids, lecithin, phospholipids, their salts, and mixtures thereof.

6. (Once Amended) A transdermal formulation as set forth in claim 1, [w] wherein the huperzine is a member selected from the group consisting of huperzine A, huperzine B, huperzine X, and salts, analogs, derivatives, prodrugs, and mixtures thereof.